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CD4+ Recovery in HIV-1 Infected Patients is Independent of Class of Antiretroviral Therapy

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *From January 1996 until May 2007 all patients in the Swiss HIV Cohort initiating their first combination antiretroviral therapy (cART) regimen, who had baseline CD4+ T-cell counts and HIV RNA levels, were included in the analysis. Of the patients, 2590 (78.7%) initiated a non-boosted protease inhibitor (PI) regimen, 452 (13.7%) initiated a nnRTI regimen, and 251 (7.6%) initiated a ritonavir-boosted PI regimen. CD4+ recovery was similar across all three groups.*

Source: Khanna N, et al. CD4+ T cell count recovery in HIV type 1-infected patients is independent of class of antiretroviral therapy. *Clin Infect Dis*. 2008;47:1093-1101.

PATIENTS ENROLLED IN THE SWISS HIV COHORT STUDY, INITIATing their first cART regimen between 1996 and early 2007, who had baseline and follow up CD4+ count and HIV RNA data available, were included in the analysis. Baseline characteristics of the patients across the three treatment groups were comparable, with the exception of lower baseline CD4 counts (168/uL) in the boosted PI group vs 201/uL in the non-boosted PI group and 220/uL in the nnRTI group. Using a primary endpoint of absolute increase in CD4 count from baseline in the three groups, the data were analyzed using a Cox proportional hazards model. Baseline determinants of CD4 count changes, which were found to be statistically significant after adjusted analysis, included age, prior antiretroviral treatment, HCV infection, baseline HIV RNA level, and prior AZT therapy (all negatively associated with response), and baseline

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CD4 count (positively associated with response). In the non-boosted PI group, CD4 increased from a median 210 to 520 cells/uL at 48 months, from a median 220 to 475 cells/uL in the nnRTI group, and from 168 to 511 in the boosted PI group. The increase in CD4 count of the three groups was not statistically significantly different. A statistically significant decrease in HIV RNA was achieved in all treatment groups after six months. HIV RNA levels decreased more rapidly in the nnRTI and boosted PI groups than in the non-boosted PI group. Virologic failure occurred in 28.7% of patients treated with non-boosted PI regimens and less frequently in the other two groups (nnRTI 11.1% and boosted PI 10.0%).

■ COMMENTARY

Some (but not all) studies comparing ART regimens in treatment-naïve patients have found smaller increases in CD4 counts in patient treated with nnRTI-based ART. This concern has, in some circles, become almost a matter of dogma, despite the fact that four large studies comparing nnRTI and PI-based cART found comparable CD4 responses.[1-4] While this study is limited by the factors inherent to all observational cohort studies, the numbers are robust, and should reassure clinicians that in the "real world" setting there is no inherent immunological advantage of boosted PI over nnRTI regimens. Another common misperception of HIV-treating physicians is that PI regimens have superior virologic efficacy to nnRTI regimens in patients with high baseline viral loads. Similarly, this is not supported by clinical trial data. ■

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Carbapenem-resistant *Klebsiella pneumoniae*

ABSTRACT & COMMENTARY

By Ellen Jo Baron, PhD, D(ABBM)

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Dr. Baron reports no financial relationships relevant to this field of study.

MOST OF US MICROBIOLOGISTS WERE RUDELY AWAKened to the insufficiency of our susceptibility testing methods last year when the College of American Pathologists (CAP) sent out a carbapenemase-producing *Klebsiella pneumoniae* as an unknown proficiency testing sample. My laboratory, like most others in the United States, incorrectly reported the isolate as susceptible to imipenem and meropenem. Hooray for CAP for helping us to recognize our failings. We now retain that strain as our internal quality control (QC) organism to run along with the patient's isolate when we perform our newly implemented susceptibility test for KPC presence (*Klebsiella pneumoniae* carbapenemase). But the invitro

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Questions & Comments

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phenotypic test for this group of enzymes is not uniformly recognized among microbiologists.

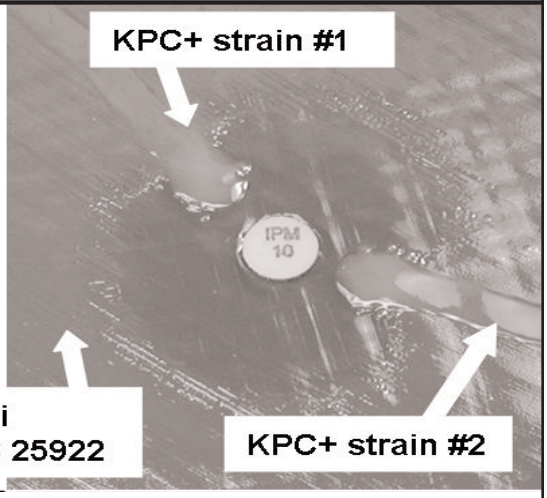
This lack of knowledge was recently addressed by a new "case study" on a widely used website devoted to antibacterial susceptibility testing.[1] Although clinicians may not be aware of it, this very useful website, dealing with susceptibility testing methods for antibacterial resistance, has been available since 2001. Initially developed by Janet Hindler (UCLA) and Fred Tenover (CDC), the site continues to provide timely case studies, protocols, and educational resources for microbiologists worldwide. The most recent addition to the site is of special interest to infectious diseases practitioners, as it outlines a laboratory method for detecting *Klebsiella pneumoniae* carbapenemases (KPCs), a rather recently expanding class of resistance factors for which there are currently no detection methods given in the reference standard that most laboratories depend on for all susceptibility testing decisions: M100-S18, the Clinical and Laboratory Standards Institute (CLSI) annually updated document, due out again in January 2009.

Laboratories in the United States that are accredited by agencies such as the College of American Pathologists, or occasionally The Joint Commission, are assured of acceptable performance ratings on their susceptibility tests if they follow the CLSI standards to the letter. Never mind that European standards set by the European Committee for Antimicrobial Susceptibility Testing (EUCAST)[2] are sometimes different, and possibly more predictive clinically, from those agreed upon by CLSI (with input from FDA), we are still effectively bound by CLSI rules. Given that CLSI standards do not include a method, many US laboratories are not testing isolates for the KPC group of enzymes, and may be erroneously reporting some organisms as susceptible to carbapenems. Case reports of treatment failures are beginning to be published.[3,4]

Carbapenemases were first characterized in the mid-1990s,[5] but they have only been recognized in clinical infections since 2001. Recently, several outbreaks in specific locales have been reported.[6] Some classes of carbapenemases (Class B) contain zinc at the active site and, are thus, termed "metallo-βeta-lactamases." In addition to Enterobacteriaceae, the carbapenemases are found in other organisms, including *E. coli* Citrobacter, Acinetobacter, Salmonella and, of particular worry, Pseudomonas aeruginosa.[7] Unfortunately, standard laboratory testing methods such as MicroScan (Dade Behring), Vitek 2 (bioMerieux), and even disk diffusion (Bauer-Kirby) do not reliably detect this resistance mechanism.[8]

What's a laboratory to do? Experts such as Dr. Kenneth Thomson at Creighton and the authors of the recent MASTER site case study recommend the modified Hodge test, also called the cloverleaf test, because the pattern of the zone of inhibition exhibited on a petri dish showing a positive result resembles a 3- or 4-leaf clover.[9] The test is performed by inoculating a fully susceptible quality control strain of *E. coli* on the standard susceptibility plate (Mueller-Hinton agar) and placing a carbapenem disk on the plate; our laboratory uses meropenem. Then freshly subcultured QC organisms, positive and negative for KPC production, are inoculated by drawing a thin line of inoculum from right next to the disk outward about 1 inch or more, usually at 90° angles to each other or on opposite sides of the disk. The test organism (unknown patient isolate) is also inoculated in a thin line outward from the disk, equidistant from the other lines. As many as four lines (two controls and two test organisms) can be drawn from one disk, hence the four-leaf clover appearance. A hint from Frans J. Robberts, a Mayo Clinic post-doctoral Fellow, is to use the sharp edge of a coverslip (not necessary that it be sterile) to draw the thinnest possible line, allowing better observation of the inward curve of the growth of *E. coli* that signifies a positive test. If the test organism produces a carbapenemase, the enzyme will diffuse into the medium around the line of growth and break down the antibiotic diffusing outward in a clean circle from the disk, allowing the *E. coli* to grow up along the line of the test organism, making a rounded corner to the zone of inhibition on either side of the line. The edge of the inhibition zone continues in a smooth circle past the line of an organism that does not produce a carbapenemase (*see Figure 1*).

Figure 1
Hodge Test



Source: Ellen Jo Baron

■ **COMMENTARY**

Although reduced susceptibility (MICs near the breakpoint, for example) of most any gram-negative rod to any carbapenem (imipenem, meropenem, ertapenem, doripenem), or resistance to a third-generation cephalosporin, are potential flags that could be used to trigger performance of the modified Hodge test, it is possible that a few strains harboring these enzymes may not exhibit either characteristic. It is the best clue we have right now, however. Clearly, laboratories will be delaying, for one day, a number of results on gram-negative rods if they implement this protocol. Implicated isolates also may produce extended-spectrum βeta-lactamases, which are detected with a separate test method.

The plethora of new resistance mechanisms is leading to the necessity for expanded susceptibility testing methods and, in some cases, slower turnaround times. Clinicians will need to exhibit patience with their microbiologists, who are scrambling to remain up-to-date and one step ahead of those crafty microbes that adapt a lot faster than we do. ■

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Inhaled Antimicrobials in the Treatment of Hospital-acquired Pneumonia

PART I OF II-PART SERIES

By Emily Cheng, PharmD Candidate, Jessica C. Song, MA, PharmD

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Emily Cheng and Jessica C. Song report no financial relationships relevant to this field of study.

HOSPITAL-ACQUIRED PNEUMONIA (HAP) REPRESENTS the second most common nosocomial infection, accounting for 15% of all hospital-associated infections.[1] Multiple parenteral antibiotic regimens have been recommended for use in the treatment of HAP patients, as illustrated in the American Thoracic Society treatment guidelines.[2] However, the treatment of HAP has been complicated by the emergence of multidrug-resistant (MDR) organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[2]

The use of antibiotics via inhalation as prophylaxis against chronic *Pseudomonas aeruginosa* pulmonary infections in cystic fibrosis patients, has been extensively reported in the medical literature.[3] At present, few studies have examined the efficacy of aerosolized antibiotics in the treatment of nosocomial respiratory tract infections. Ioannidou et al conducted a meta-analysis of five randomized, controlled trials that compared inhaled (or endotracheally instilled) antibiotics (tobramycin, 3 trials; sisomycin, 1 trial; gentamicin, 1 trial) with control treatment (placebo, 4 trials; intramuscular gentamicin, 1 trial).[4] Administration of aminoglycosides via the respiratory tract improved treatment success in the intention-to-treat patients (odds ratio = 2.39, 95% CI, 1.29 to 4.44).

To date, small case studies and larger studies have evaluated the efficacy of colistimethate (Coly-Mycin), amikacin, tobramycin, and ceftazidime in the treatment of HAP/VAP (ventilator-associated pneumonia) patients.[5-9] In addition, aerosolized amphotericin B deoxycholate and liposomal amphotericin B (AmBisome) have been studied for use as prophylaxis against invasive Aspergillosis infections.[10-12]

This two-part review (part II will come in a future issue) will discuss the use of inhaled antibiotics in the treatment of HAP/VAP, along with the use of aerosolized amphotericin B for prophylaxis of invasive fungal infections in

patients at high risk for acquiring these infections. Part I will highlight aerosolized colistimethate and amphotericin B. Part II will continue with a discussion on aerosolized tobramycin, amikacin, and ceftazidime.

Part I: Colistimethate and Amphotericin B

Administration of Inhaled Colistimethate and Amphotericin B (Deoxy Cholate/Liposomal)

Inhaled antibiotics may be more valuable than intravenous antibiotics in the treatment of HAP for several reasons. Direct delivery of antibiotics to the lungs results in higher concentrations at the site of infection and increased drug efficacy.[5,6] Also, local administration reduces the risk of systemic toxicity. The most common adverse reaction associated with inhaled antibiotics is bronchospasm.[5] Administration of a short-acting b2-agonist bronchodilator (albuterol) before inhalation therapy can mitigate this side effect.

Parenteral colistimethate is indicated for the treatment of infections caused by gram-negative bacteria, but is infrequently used because of its association with nephrotoxicity and neurotoxicity.[13] European studies have primarily utilized the prodrug colistimethate sodium (ColyMycin) rather than colistin sodium because it is better tolerated and easier to prepare for inhalation.[5,7,8] Aerosolized solution can be prepared by reconstituting one vial of colistimethate for injection in a suitable volume (usually 4-5 mL) of normal saline or sterile water and placing it into a nebulizer.[13] Colistimethate studies have used a dosing range of 1.5 to 6 million IU per day (12,500 IU is equal to 1 mg), divided into 2-4 doses.[5,7,8] When administered via inhalation, colistimethate is most commonly associated with bronchoconstriction, which can be prevented with pretreatment. Severe adverse effects such as nephrotoxicity and neurotoxicity are rare. There has been one reported death associated with aerosolized colistimethate. When the prodrug colistimethate is mixed with water, it undergoes hydrolysis, creating two forms of the active drug, one of which is toxic to lung tissue. The concentration of this metabolite increases with time, and can result in severe pulmonary and systemic toxicity. Thus, colistimethate for inhalation should be used within 24 hours of preparation.[13] For Santa Clara Valley Medical Center's protocol on aerosolized colistin, refer to *appendix I* below.

Intravenous amphotericin B is indicated for the treatment of numerous fungal infections. Like colistimethate, intravenous amphotericin B is associated with systemic toxicity, which can be avoided with aerosolized formulations. Inhalation solutions of amphotericin B deoxycholate and AmBisome® can be prepared by reconstituting the vial of powder for injection with sterile water. For amphotericin B deoxycholate, solutions of 2 mg/mL and 10 mg/mL have been used for inhalation in clinical studies.[10,12] AmBisome® can be reconstituted to a concentration of 5 mg/mL.[11] After reconstitution, these solutions can be placed in a nebulizer for use.

Clinical Trials of Colistimethate and Amphotericin B

Aerosolized colistin/colistimethate has been studied as an adjunctive measure to parenteral antibiotics in the treatment of *P. aeruginosa* and *A. baumannii* infections. Berlana et al studied the effects of inhaled colistimethate on the clearance of causative organisms from sputum, urine, blood, and CSF.[7] Concurrent systemic antibiotics were given to 73% (53 out of 80) of patients. Results showed aerosolized colistimethate to be both efficacious and safe. Michalopoulos et al studied inhaled colistimethate as an adjunct to intravenous levofloxacin, co-trimoxazole, ciprofloxacin, meropenem, tobramycin, aztreonam, or gentamicin.[8] This study also found inhaled colistimethate to be beneficial in combination with IV antibiotics against MDR HAP. The details of these studies can be found in *Table 1*.

Inhaled amphotericin B has been studied as prophylaxis against aspergillosis in immunocompromised patients. Posaconazole is indicated for prophylaxis of Aspergillus and Candida infections in immunocompromised patients, but has been shown to interact with multiple drugs, and should be used with caution in patients with impaired hepatic function.[14,15] Dubois et al studied the physiologic effects of inhaled amphotericin B after a mean of 4.98 treatments in granulocytopenic patients. They found that aerosolized amphotericin B deoxycholate is generally well-tolerated, with few mild adverse reactions such as nausea, vomiting, and cough.[10]

Rjinders et al performed a trial using aerosolized liposomal amphotericin B (AmBisome®) in neutropenic patients who received prior fluconazole prophylaxis.[11] During the treatment period for patients given aerosolized AmBisome® and placebo, inhaled AmBisome® resulted in lower incidence of invasive Aspergillus infection (4% vs 14%, $p = 0.005$).

Schwartz et al conducted a study using inhaled amphotericin B deoxycholate for prophylaxis against invasive aspergillosis in patients with prolonged neutropenia. In this study, antibacterial prophylaxis was administered to some patients, and oral antifungals (amphotericin and fluconazole) were allowed for prophylaxis against Candida species. In contrast to the findings of Rjinders et al, Schwartz et al failed to demonstrate the prophylactic efficacy .....*continued on p. 44*

Table 1

Inhaled Efficacy of Inhaled Colistimethate Sodium

Investigators	Study Design/Primary Endpoints	Patients	Primary Findings

Berlana, et al[7]	Retrospective, single center, single agent
	
	Dose/duration:
	Acinetobacter baumannii:
	• Colistimethate 0.5 MU q6hr – 1 MU q8hr for 12 ± 8 days inhalation
	• Colistimethate 1 MU q12hr – 2 MU q8hr for 11±6 days IV/IM
	• Colistimethate 10mg q12hr for 8-10 days intrathecal
	Pseudomonas aeruginosa:
	• Colistimethate 0.5 MU q6hr – 1 MU q8hr for 12±8 days inhalation
	
	Primary endpoint:
	clearance of causative organism
		80 patients total (71 courses colistin)
		Isolate location:
		• 71 (89%) sputum, aspirate, bronchoalveolar lavage
		• 7 (9%) urine
		
		Location:
		• 67 (84%) ICU
		• 13 (16%) medical surgical ward
		
		Administration route
		Acinetobacter baumannii:
		• Inhalation: 60 patients
		• IV/IM: 12
		• Intrathecal: 2
		Pseudomonas aeruginosa:
		• Inhalation: 11 patients
		
		Concomitant antibiotics
		• 64 (80%) at least 1 other antibiotic before colistin:
		  • 17 (21%) Imipenem/Cilastatin
		  • 14 (18%) Amoxicillin/Clavulanic Acid
		• 58 (73%) received at least 1 other antibiotic during colistin
		  • Carbapenems (35%)
		
		Isolate
		• 69 (86%) *Acinetobacter baumannii*
		• 11 (14%) *Pseudomonas aeruginosa*
			Clearance of causative organism:
			Acinetobacter baumannii (inhalation)
			• Negative: 33 of 33 cultures (100%)
			• Positive: 0%
			Pseudomonas aeruginosa (inhalation)
			• Negative: 4 (57%)
			• Positive: 3 (43%)
			
			Mortality: 14 (18%)
			
			Sensitivities:
			Acinetobacter baumannii:
			• 41 (59%) patients only sensitive to colistin
			• 70 (100%) patients sensitive to colistin
			Pseudomonas aeruginosa:
			• No patients were only sensitive to colistin
			• 11 (100%) patients sensitive to colistin
			
			Renal toxicity
			• IM/IV therapy did not result in significant changes in BUN/SCr.

Michalopoulos, et al[8]	Retrospective, single center, single agent
	
	Dose/duration:
	• 1.5-6 MU/day of aerosolized colistimethate in 3-4 divided doses administered for a mean of 10.5 days (3-32 days)
	• Delivered by Siemens Servo Ventilator 300 in ventilated patients
	• Delivered via face mask for spontaneously breathing patients
	
	Primary endpoint
	Positive outcome (cure or improvement) of pneumonia based on clinical, radiological, and laboratory findings
		8 patients total
		• One infection due to *P. aeruginosa*
		• Seven infections due to *A. baumannii*
		• Received colistimethate for multidrug-resistant gram-negative bacteria between 10/2000 and 1/2004 at Henry Dunant Hospital in Athens, Greece
		• Admitted to ICU with mean Acute Physiology and Chronic Health Evaluation II scores of 14.6 at admission and 17.1 on day 1 of colistin therapy
		• All patients had mechanical ventilatory support for a mean of 19.4 days
		• All received prior antimicrobials before colistimethate was initiated
		• 3/8 patients treated with immunosuppressive therapy
		• 4/8 patients received immunoglobulin therapy during hospitalization
		• Mean age 59.6 years
		• 6/8 patients were male
			• Pneumonia responded to treatment in seven of the eight patients
			  • four cured episodes
			  • three improved episodes
			  • Remaining 1 patient deteriorated and died, but had many underlying diseases (hypertension, chronic renal insufficiency)
			• Follow-up cultures were available for five of the eight patients
			  • four patients had eradication of pathogen
			  • Pathogen persisted in 1 patient, who subsequently died
			• No superinfection with gram-positive bacteria or yeasts
			• No gram-negative bacteria developed resistance to colistimethate
			• Aerosolized colistimethate was well tolerated. No patients experienced chest tightness, bronchoconstriction, or apnea
			  • two patients with a history of COPD received B2 agonist
			• Renal function did not worsen except for one patient who had prior renal dysfunction

Table 2

Clinical Efficacy of Inhaled Amphotericin B

Investigators	Study Design/Primary Endpoints	Patients	Primary Findings

Dubois, et al[10]	Prospective, single center, single agent
	
	Dose/duration
	• 3 mL of 10 mg/mL solution delivered via Respirgard II nebulizer using oxygen at a flow rate of 6 L/min
	• Amphotericin inhalations discontinued if granulocytes rose to > 500/mL, Scr rose to over 1.0 mg/mL, there was evidence of a systemic reaction (hypotension, tachycardia, rigors), or if IV amphotericin therapy was initiated
	
	Primary endpoint
	• Assessment of respiratory effects of inhaled amphotericin B
	  • oxygen saturation monitored throughout therapy
	  • peak flow values measured before and after therapy
	  • cough and dyspnea rated by patients using Borg scale
		18 patients enrolled in study (mean of 4.98 treatment courses/patient)
		• Inclusion criteria
		  • granulocytopenia (< 500 granulocytes/mm^3) projected to last > 2 weeks
		  • expected life span >2 weeks
		  • ability to give informed consent
		  • ≥18 years of age
		  • lack of fever
		• Exclusion criteria
		  • prior history of fungal infection
		  • history of severe asthma
		  • treatment with amphotericin B at time of possible enrollment
		  • history of anaphylactic response to amphotericin B
		  • Scr > 2mg/dL
		  • refusal to sign informed consent
		• 18 bone marrow transplant patients
		• 2 patients that underwent leukemic induction therapy
		• Patients stopped therapy, due to
		  • granulocytes > 500/mL
		  • vomiting
		  • became comatose
		  • mucositis
			• The mean arterial oxygen saturation level was 97% at onset and 98% at the end of therapy, with the largest drop being 4%
			• Mean peak flow dropped from 539 L/min before therapy to 520 L/min after ($p < 0.001$)
			  • 9 instances of clinically significant drop in peak flow (drop of 20% or more), four of which occurred in asthmatic patients
			  • significant drop in peak flow with 21% of treatments given to asthmatic patients vs 4.4% of patients without asthma
			• Amphotericin therapy associated with dyspnea and cough
			  • mean Borg scale rating for cough went from 0.4 ± 0.7 before therapy to 0.9 ± 1.5 after ($p < 0.001$)
			  • cough increased by more than 2 Borg descriptors for 9 treatments
			  • mean Borg scale rating for dyspnea went from 0.3 ± 0.7 to 0.7 ± 1.2 after treatment ($p < 0.001$)
			  • dyspnea increased by more than two Borg descriptors in three cases

Rijnders, et al[11]	Randomized, double-blind, placebo-controlled trial
	
	Dose/duration
	• 2.5 mL of a 5 mg/mL solution of liposomal amphotericin B (AmBisome®)
	• Placebo
	• Nebulized for 30 minutes/day on two consecutive days per week until neutrophil recovery (ANC > 300 cells/mm3), with a maximum of 12 inhalations per neutropenic episode
	• Nebulization performed with an adaptive aerosol delivery system (Halolite AAD or ProDose AAD)
	
	Primary endpoint
	• Occurrence of invasive pulmonary aspergillosis according to European Organization for Research and the Treatment of Cancer-Mycoses Study Group (EORTC-MSG) definitions
	
	Other endpoints
	• Overall mortality
	• Invasive pulmonary aspergillosis-related mortality
	" Safety
		271 patients enrolled in the study (139 received amphotericin, 132 received placebo)
		
		• Inclusion criteria
		  • adult with hematologic disease hospitalized at Erasmus Medical Center in the Netherlands
		  • had to start chemotherapy within seven days after enrollment with anticipated duration of neutropenia (ANC < 500 cells/mm^3) for ≥ 10 days
		  • received prophylactic fluconazole
		
		• Exclusion criteria
		  • evidence of fungal infection in lung or sinuses at onset of trial
		  • unable to use nebulizer
		  • expected survival < 3 months
		  • previous intolerance to amphotericin B
		
		• Hematologic and clinical characteristics between the two treatment groups was balanced
			• Development of invasive pulmonary aspergillosis occurred in 4% of amphotericin-treated patients and 14% of placebo patients ($p = 0.005$)
			• Within 28 days of neutrophil recovery, seven patients died from the amphotericin group (none were aspergillosus-related deaths). In the placebo group, six patients died (one was aspergillosis-related).
			• Median Scr levels after the last inhalation were not greater than the baseline level in amphotericin-treated patients.
			• Treatment was discontinued if the patient was too weak to use the aerosol system or if the patient experienced technical problems with the system.
			• Aerosolized amphotericin was generally well tolerated. Coughing during inhalation occurred in 16 patients of the amphotericin group and 1 patient of the placebo group ($p = 0.02$).
			• No serious adverse effects or systemic toxicities were reported.

of aerosolized amphotericin B deoxycholate against the development of invasive Aspergillus infection. *Table 2* outlines the key data regarding the efficacy of aerosolized amphotericin B as prophylaxis for invasive Aspergillus infection.

Conclusion

As MDR organisms become more prevalent in the hospital setting, inhaled antimicrobials may be considered as a treatment option. Direct administration of antimicrobials to the lungs, in combination with parenteral antimicrobials, may enhance clinical outcomes, and does not appear to be associated with systemic toxicity. Clinical studies of inhaled colistimethate show that it is beneficial against *P. aeruginosa* and *A. baumannii* pneumonia. While the studies of inhaled amphotericin have yielded mixed results, this antifungal class may still represent an option for the prevention of fungal infections in immunocompromised patients who are unable to tolerate azole antifungals or echinocandins. ■

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APPENDIX I

Policy: Aerosolized Colistin may be used to treat acute or chronic pulmonary infections secondary to multi-drug resistant *Pseudomonas aeruginosa* or other susceptible bacteria refractory to conventional therapy (oral and IV medications). Aerosolized Colistin must be delivered via a closed nebulizer system or in the hood in the Respiratory Care Special Procedure Room. A Pulmonary Attending order/approval is mandatory.

Responsible Party: Respiratory Care
Action:

1. Review patient's chart for:
   A. Admitting diagnosis
   B. Patient's history and appropriate laboratory data
   C. Order for Colistin "150 mg BID" via PARI LC PLUS Filtered Nebulizer. Order must be by Pulmonary Attending Only.
2. Verify that the patient has signed an informed con sent form for non-FDA approved delivery of Colistin.
3. Contact Pharmacy to inform them of order for Colistin.
4. Obtain medication from Pharmacy. (Any questions regarding the reconstitution of the Colistin, please contact the Pharmacy).
5. Gather equipment:
   A. Flowmeter

B. PARI LC PLUS Filtered Nebulizer System
C. Nose clips or aerosol mask if indicated
D. Ordered antibiotic
E. Hand-held nebulizer
F. Bronchodilator

6. Introduce yourself to the patient.
7. Wash your hands.
8. Check patient identification wristband.
9. Explain procedure to patient.
10. Assemble and check equipment for proper function.
11. Administer Albuterol treatment via Respiratory Care Small Volume Nebulizer Procedure B7180-29. (Administer Alupent or Atrovent if contraindications to Albuterol exist).
12. Upon completion of the bronchodilator treatment place contents of the antibiotic vial into the PARI LC PLUS Filtered Nebulizer System.
13. Place patient in the hood in the Special Procedure Room or verify that patient is in single patient room.
14. Perform patient assessment. Assessment to include but not limited to:

A. Respiratory Rate
1. Hold for Respiratory Rate ≥ 25/minute
B. Breath sounds — aeration, wheezes, rhonchi, rales and locations in lungs
C. Pulse (Additionally checked mid-therapy)
1. Hold or stop therapy for:
a. Pulse greater than 120/minute or limits ordered by physician
b. Increase in pulse with treatment greater than 20/minute
c. Notify MD/Nurse of these conditions and "the holding" of therapy
D. Respiratory effort — easy, unlabored, dyspneic, SOB, use of accessory muscles, retractions
E. Chest expansion — good, improved, equal
F. Cough effort — good, poor, splinting
G. Sputum — color, quantity, viscosity
H. Patient indicated response (when possible)
I. Subjective evaluation of response — no apparent distress, relief from SOB, tolerated well
J. Adverse reactions
K. Mental status/behavior — uncooperative, combative, agitated, cooperative

15. Have patient place mouthpiece into his/her mouth and adjust flow of gas for a continuous, dense mist. (Approximately 6-8 LPM).
16. Instruct the patient to breathe through their mouth until all the medication has been nebulized.
17. At the end of the treatment, have the patient rinse their mouth with water.
18. Shake out the PARI LC PLUS Filtered Nebulizer System and store in patient storage bag.
19. Perform patient assessment as before.
20. Chart in Medi-Serve. Charting should include but is not limited to the following:

A. Respiratory Rate
B. Breath sounds — aeration, wheezes, rhonchi, rales and locations in lungs
C. Pulse
D. Respiratory effort — easy, unlabored, dyspneic, SOB, use of accessory muscles, retractions
E. Cough effort — good, poor, splinting
F. Sputum — color, quantity, viscosity
G. Patient indicated response (when possible)
H. Adverse reactions
I. Drug and dose administered, and how tolerated

21. Patient must remain in closed isolation room for one hour after treatment, any person entering the room during the treatment or within one hour of the Colistin treatment must wear a TB isolation mask.
22. Adverse reaction:

A. Bronchospasm

Serial Dilution of Inhalation Sulfite Challenge

A serial dilution of decreasing concentrations of Colistin will be mixed by the pharmacy for the Inhalation Sulfite Challenge.

• Start with 1 mL of 150 mg/mL solution of Colistin mixed with 9 mL of normal saline (NS) to come up with 15 mg/1 mL solution. This will be sample 4.

• Withdraw 1 mL from Sample 4 and mix with 9 mL of NS to come up with 1.5 mg/1 mL solution. This will be sample 3.

• Withdraw 1 mL from Sample 3 and mix with 9 mL of NS to come up with 0.15 mg/1 mL solution. This will be sample 2.

• Withdraw 1 mL from Sample 2 and mix it with 9 mL of NS to come up with 0.015 mg/1 mL solution. This will be Sample 1.

Medication will be administered serially in increasing concentrations as follows:

Sample 1	0.015 mg/mL
Sample 2	0.15 mg/mL
Sample 3	1.5 mg/mL
Sample 4	15 mg/mL

Source

Appendix I is Santa Clara Valley Medical Center's protocol on aerosolized colistin.

Resource

1. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant

Pseudomonas aeruginosa with aerosolized colistin. *Am J Respir Crit Care Med*. 2000;162:328-330.

CME Questions

10. Which of the following is correct with regard to treatment of HIV infection in the Swiss Cohort?

a. Non-boosted protease inhibitor-based regimens were associated with inferior CD4 T cell responses when compared to other regimens.
b. Boosted protease inhibitor-based regimens were associated with inferior CD4 T cell responses when compared to other regimens.
c. Non-nucleoside analog reverse transcriptase inhibitor (nnRTI)-based regimens were associated with inferior CD4 T cell responses when compared to other regimens.
d. Non-boosted protease inhibitor-based regimens were associated with inferior virological responses when compared to other regimens.

11. Which of the following is correct?

a. The presence of a carbapenemase is readily detected by routine in vitro susceptibility testing.
b. The presence of a carbapenemase is readily detected by the E-test.
c. The presence of a carbapenemase by the Hodge test.
d. Enterobacteriaceae do not require evaluation for the presence of carbapenemases since they do not carry these enzymes.

12. Which of the following is correct?

a. The most commonly encountered side effect associated with receipt of antibiotics by inhalation is bronchospasm.
b. Scientifically sound prospective randomized clinical trials have demonstrated that the optimal treatment of Gram negative pneumonia is by the administration of colistin by inhalation without a need for parenteral antibiotic therapy.
c. Scientifically sound prospective randomized clinical trials have demonstrated that the optimal treatment of *Aspergillus pneumonia* is by the administration of amphotericin B without a need for parenteral antifungal therapy.

Answers: 10. (d); 11. (c); 12. (a)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

CME Instructions

Physicians participate in this CME program by reading the issue, using the references for research, and studying the questions. Participants should select what they believe to be the correct answers, then refer to the answer key to test their knowledge. ■

In Future Issues:

***Kingella kingae* Infections in Children**

UPDATES

By Carol A. Kemper, MD, FACP

WNV infection and the mortgage crisis

Source: Reisen Wk, et al. Delinquent mortgages, neglected swimming pools, and West Nile Virus, California. *Emerg Infect Dis*. 2008,14:1747-1749.

An outbreak of 140 human cases of West Nile Virus in Kern County, California (better known for its increased risk of coccidioidomycosis), during the summer of 2007, prompted Reisen et al to look for possible causes. Based on vector control data, there was a significant increase in WNV infection in birds in the area in June 2007, shortly followed by human cases. A total of 124 dead birds were identified, many of which were young hatchlings, which have limited immunity to WNV. Mosquito traps in June also showed a spike in WNV-infected female mosquitoes (18.5 infected mosquitos/1000).

Searching for an answer to the increased prevalence of WNV, an aerial map of Bakersfield showed a number of green pools and Jacuzzi/hot tubs in people's backyards. Based on aerial photos taken in August 2007, at least 17% of 42 pools in the immediate Bakersfield area were green. Reisen et al speculate that delinquent mortgages and abandoned homes were to blame for the neglected pools — delinquencies in the area were up 300% in 2007 compared with a year earlier.

In addition, Reisen et al note that many regulations and laws requiring owners to keep pools locked up, keep these same pools out of reach of local mosquito abatement personnel. Ordinances in our area require a surrounding 2M fence, with a locked gate, or a secured locked pool cover, so that rascals may not access the pool when the owner is not present. (In fact, I almost did not pass a recent re-roof inspection with our county because I had an "unsecured" hot tub lid.

All of these city and county regulations make it impossible for vector control/mosquito abatement personnel to access those bodies of water in back yards. Another possible theory to the green pools? How about people too busy working to attend to their own pools, or pay the monthly fees for regular pool maintenance. Or, how about those increased summertime temperatures (global warming?) coupled with an increase in phosphates in the hose water, used to fill the pool over the hot summer?

Effect of post-partum HIV treatment discontinuation

Source: Onen NF, et al. Effect of post-partum HIV treatment discontinuation on long-term maternal outcome. *J Int Assoc Physicians AIDS Care*. 2008;7: 245-251.

Longer term outcomes of HIV-infected women who continue antiretroviral therapy post-partum were compared with that of women who did not continue treatment. A total of 172 pregnancies occurring between 1997-2005 were examined. The median duration of follow-up was 32 weeks. Post-partum discontinuation of antiretroviral therapy occurred in 123 (71.5%) women. A total of 12 opportunistic infections and 2 deaths occurred, a significant number of which were observed in women no longer receiving ART (including 10 OIs and both deaths).

Unfortunately, information on CD4 cell counts and the need for ART based on other factors was not available. (Attempts to download the article were met with a request for $30 to view the article online for one day). Since pregnancy is, to some degree, an immune suppressive state, it is conceivable that the combined effects of pregnancy and HIV status may be additive, and require a more aggressive treatment response during the post-partum period. Without more information, these data suggest that women who discontinue ART post-partum may not do as well as their counterparts who continue treatment. Additional information and study would be helpful in defining recommendations for treatment in HIV-infected woman who have recently delivered. ■

Thousands of years later — a new kind of leprosy

Source: ProMED-mail post November 24, 2008; www.promedmail.org

Diffuse lepromatous leprosy (DLL) is an especially virulent form of multibacillary disease, occasionally seen in patients from Central and South America

and Southeast Asia. Lucio's phenomena is a highly anergic and more severe form of DLL, resulting in extensive skin and subcutaneous involvement, with an abundance of organisms infiltrating tissues. Dermal infarcts occur, occasionally resulting in extensive necrosis, with histopathologic evidence of obliterative vasculitis of dermal and subcutaneous vessels. These extensive skin lesions increase the risk for superinfection and sepsis.

These authors from MD Anderson report on two such cases occurring in 2002 and 2007 at their facility, the first of which was so severe as to prompt transfer to the burn unit. The second occurred in an older Latino from Mexico, who presented with extensive skin lesions on his lower extremities. Within days, he became septic and died. Autopsy confirmed the presence of DLL, with diffuse AFB infiltrating blood vessels.

Having done gene sequencing on other organisms, the authors turned their hand to the organisms responsible for these two cases. Sequences of the 16S ribosomal subunit and five other genes were examined and compared to other mycobacterial cases, including *M. leprae.* The 16S ribosomal sequences were only 97.9% homologous with *M. leprae* — a huge difference, considering that gene sequences in other cases of leprosy are essentially identical. The five other genes reportedly showed important differences as well. The strain identified from these two individuals constitutes a new strain of leprosy — called *M. lepromatosis*.

Analysis of tissue from two other similar cases of DLL occurring in Singapore, yielded this same organism. All four patients died of their disease. While its distribution worldwide has not yet been determined, the discovery of this new mycobacterial organism may explain some of the variation seen in cases of leprosy.

Screening and treatment of TB in immigrants

Source: Cain KP, et al. Tuberculosis among foreign-born persons in the United States. *JAMA*. 2008;300: 405-412.

Slightly more than half of the cases of active TB occurring in the United States between 2001 and 2006 were reported among foreign-born persons. In all, 47,000 cases of TB were reported among foreign-born persons in the United States during this period. Twenty-eight percent of these cases occurred in recent immigrants (< 2 years from entry), although even persons who had lived in the United States for more than 20 years remain at risk for reactivation of their infection.

The highest rates of reactivation TB occurred in individuals from sub-Saharan Africa (> 250 cases per 100,000 persons), somewhat greater than individuals from Central America (> 100,000 cases per 100,000 persons). Increased age at entry to the United States increased the risk of reactivation disease.

Resistant TB was also greater in persons who were foreign-born. INH resistance was observed in persons from Vietnam (20%), Peru (18%), the Philippines (17%), and China (16%). Persons from either Peru or China were at significant risk of multidrug-resistant disease (6%).

For this reason, it is incumbent on primary care physicians to step-up surveillance of latent TB and treatment of LTBI in persons who are foreign-born, even if these patients have lived in the United States for many years. Many of these patients do not recognize the risk that TB poses to themselves, their families and their colleagues at work, and too often discount their skin test as "old news," or as the result of prior BCG vaccination.

Current public health guidelines recommend 9-12 months of treatment for all of these individuals, regardless of age or length of stay in the United States. I recommend a two-step PPD for all non-BCG-vaccinated persons; the sensitivity and specificity is comparable to the gamma-interferon-based (GIB) assays (approximately 96% specific). In persons who have received BCG, or in whom there is some question of previous vaccination, a GIB assay is more specific than PPD (meaning fewer false positives).

I find it is helpful to phrase the risks, when speaking to patients, as follows: the lifetime risk of reactivation disease in someone with a positive skin test or GIB assay is approximately 7% (or 1 in 13). This lifetime risk is biphasic, and greatest during the two years following exposure and with increasing age. This risk roughly increases to 20% (or 1 in 5) if they have an abnormal chest radiograph consistent with old, healed granulomatous disease. Should they require chemotherapy or steroids or other immunosuppressive therapy, the risk increases to approximately 20% in 3-6 months. Chronic disease, such as diabetes and renal failure, also increase the risk of reactivation disease. Now, ask your patients, who would want to take this risk and possibly exposure their children or their colleagues at work to TB? ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

JUPITER: C-reactive Protein a Marker for CV Events?

In this issue: The JUPITER trial causes a stir; ACP practice guideline for antidepressant use; testosterone for low libido; continued shortage of Hib vaccine; FDA Actions.

The JUPITER trial causes a stir

Elevated high-sensitivity C-reactive protein (CRP) may help identify otherwise healthy patients with normal cholesterol levels who will benefit from statin therapy, according to the JUPITER trial published in November. Researchers randomized nearly 18,000 healthy men and women with normal cholesterol levels (LDL < 130 mg/dL) with CRP levels of 2.0 mg/L or greater to rosuvastatin (Crestor) 20 mg daily or placebo. The combined primary endpoint was myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular cause. The trial was stopped early at 1.9 years when the rate of the primary endpoint was found to be 0.77 per 100 person-years in the treatment group vs 1.36 per 100 person-years in the placebo (HR 0.56; 95% CI, 0.46-0.69; $P < 0.00001$). Overall, the rate of events was low in both groups: 142 of 8901 in the treatment group vs 251 of 8901 in the placebo group. The individual endpoints of myocardial infarction, stroke, and revascularization or unstable angina were all reduced by approximately 50% in the rosuvastatin group, LDL cholesterol levels were decreased by 50%, and CRP levels were decreased 37%. There was not a significant increase in myopathy or cancer in the treatment group, but there was a higher incidence of physician-reported diabetes. The authors conclude that in apparently healthy persons without hyperlipidemia but with elevated CRPs, rosuvastatin significantly reduced the incidence of major cardiovascular events (*N Engl J Med* 2008;359:2195-2207).

In an accompanying editorial, Mark Hlatky, MD, Stanford University School of Medicine, points out that although the relative risk reductions in the JUPITER trial were clearly significant, the absolute difference in risk was less impressive with 120 participants treated for 1.9 years to prevent one event. It is also difficult to know the role of CRP in risk stratification since patients with normal CRP levels were not treated and it is possible that lowering cholesterol with statins may benefit even those with low CRP levels. CRP may have a role in deciding whether to treat patients with intermediate risk, but it may be too early to use it to recommend treatment for those at low risk. Hlatky writes that "guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and long-term safety and cost" (*N Engl J Med* 2008;359:2280-2282). It is safe to say that JUPITER has been the subject of many lively discussions in hospital lunchrooms

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

across the country. Whether the benefit of rosuvastatin can be generalized to all statins, whether CRP should be a standard part of yearly blood panels for adults patients, and whether everyone with an elevated CRP should be offered treatment with a statin are all questions that are being hotly debated and will need further evaluation.

ACP treatment guideline for antidepressants

The American College of Physicians has issued a practice guideline for the use of antidepressants to treat depressive disorders. The guideline encompasses the use of newer "second-generation antidepressants," including the SSRIs: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox). Also included were the SNRIs venlafaxine (Effexor), and duloxetine (Cymbalta), as well as other drugs such as mirtazapine (Remeron), bupropion (Wellbutrin), nefazodone, and trazadone. After reviewing 203 clinical trials, the guideline group concluded that there were no significant differences between the drugs with regard to efficacy. The guideline group recommends that second-generation antidepressants should be selected on the basis of adverse effect profiles, cost, and patient preference. They further recommend that clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1-2 weeks of initiation of therapy and that treatment should be modified if the patient does not have an adequate response to pharmacotherapy within 6-8 weeks. Finally, they recommend that clinicians continue treatment for 4-9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients with history of depression, a longer duration of therapy may be beneficial (*Ann Intern Med* 2008;149:725-733).

Testosterone for low libido: Questions remain

Low sexual desire is commonly reported by postmenopausal women. A new study suggests that testosterone replacement may be of benefit. Researchers randomized 814 postmenopausal women with hypoactive sexual desire or disorder to testosterone patches delivering 150 or 300 mg of testosterone per day or placebo. The primary endpoint was change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes. Safety outcomes were followed out to one year. At 24 weeks the primary endpoint was significantly greater in the group receiving 300 mg of testosterone per day than placebo (increase in sexually satisfied episodes of 2.1 vs 0.7, $P < 0.001$) but not in the group receiving 150 mg per day. Both doses of testosterone were associated with significant increases in desire and decreases in distress. The rate of androgenic side effects including unwanted hair growth was higher in the group receiving 300 mg per day. Breast cancer was diagnosed in 4 women who received testosterone vs none in the placebo group. The authors conclude that a testosterone patch delivering 300 mg per day results in modest but meaningful improvement in sexual function although the long-term effects of testosterone including effects on the breasts remain uncertain (*N Engl J Med* 2008;359:2005-2017). This study confirms previous reports that testosterone has a positive effect on sexuality in women. The rate of breast cancer, although not reaching statistical significance in this study, raises concern.

Continued shortage for Hib vaccine

The continued shortage of the *Haemophilus influenza* type b (Hib) vaccine has not led to an increase in *Haemophilus* infections according to the *MMWR*. It has been a year since the CDC recommended deferring the fourth dose of the Hib vaccine in healthy children (at 12-15 months of age) because of a shortage due to contamination concerns in the manufacturing process. Merck & Co. now reports that mid-2009 is a realistic date for normal production. The CDC has undertaken national surveillance for Hib infections including 748 cases in children < 5 years old. Of these, only 6% were clearly identified as serotype b (the most invasive strain of *Haemophilus*), although serotyping information was missing in nearly 40% of cases. The CDC is concerned because antibody levels fall 12 months after vaccination in children. In the U.K., where the fourth booster was not initially recommended, Hib infections rebounded after 12-15 months. CDC is recommending vigilance on the part of pediatricians and also is emphasizing that state and hospital labs should perform serotyping on all *Haemophilus* infections.

FDA Actions

The FDA has approved fesoterodine fumarate for the treatment of overactive bladder. The drug relaxes smooth muscle of the bladder reducing urinary frequency, urge to urinate, and sudden urinary incontinence. Fesoterodine fumarate will be available in 4 mg and 8 mg strengths for use once daily. The drug is manufactured by Schwartz Pharma and will be marketed as Toviaz . ■